Cancer induced Coagulation

57. JAHRESTAGUNG
Gesellschaft für Thrombose- und Hämostaseforschung (GTH)

57TH ANNUAL MEETING
of Thrombosis and Haemostasis Research

Armand Trousseau
1801 – 1867
„Trousseau Syndrome“

Theodor Billroth
1829 - 1894
„Thrombosis – a Symptom of Metastases“

Harold F Dvorak
„Wounds that do not heal“

Deep vein thrombosis (DVT) and pulmonary embolisms (PE) in 4,077 consecutive post - mortem series (1979 - 1989)

Saeger et al Path. Res. Pract 1994

966 CASES OF DVT/PE (27.7%) WERE DIAGNOSED and IN 54.5 % OF CASES MALIGNANCY WAS PRESENT.

most frequent cancer types	cases with DVT/PE (n=966)	control group without DVT/PE (n=350)
GASTRIC CANCER	10.0 %	6.6 %
BREAST CANCER	5.7 %	3.1 %
PANCREATIC CANCER	5.6 %	2.6 %
UTERINE CANCER	2.4 %	0.6 %
HEPATIC CANCER	0.8 %	2.3 %

Thrombosis and Cancer

Rickles FR, Edwards RL Blood 1982:62; 14-31

Tumor Type	*(n)*	rel.(%)
Lung	*139*	25.6
Pancreas	*94*	17.4
Stomach	*91*	16.8
Colon	*82*	15.2
Prostate	*35*	6.5
Ovary/Uterus	*34*	6.3
Gallbladder	*15*	2.8
Breast	*11*	2.0
Kidney	*2*	0.4
Other and unknown primary	*37*	7.0
Total	*541*	100

Venous thromboembolism and cancer

Baron et al Lancet 1998;351:1077-80

Standardised incidence ratio (SIR) of cancer in 61,998 patients admitted to hospital for DVT from 1965 - 1983 (recorded from the Swedish Cancer Registry) compared to the Swedish national cancer rates of the same period.

	cancer diagnosis at the time of DVT or first year afterwards SIR (95%)	cancer diagnosis 2 years and more after DVT admission SIR (95%)
all cancer:	4.4 (4.2 - 4.6)	1.3 (1.3 - 1.3)
breast:	1.8 (2.8 - 6.3)	1.2 (1.1 - 1.3)
cervix:	4.3 (2.8 - 6.3)	1.1 (0.8 - 1.4)
endometrium:	4.4 (3.2 - 5.7)	1.2 (1.0 - 1.5)
ovary:	11.4 (9.6 - 13.4)	1.2 (1.0 - 1.4)

Thrombosis – an Announcement of Cancer

Aderka	1986 Cancer	16.9 %	4-36 months
Gore	1982 Ann Int Med	14.7 %	0-24 months
Monreal	1988 Chest	12.5 %	not defined
Monreal	1991 Cancer	10.6 %	0-12 months
Bastounis	1996 J Int Med	10.1 %	0-12 months
Prandoni	1996 Ann Int Med	8.7 %	not defined
Rajan	1998 Thromb Haemost	8.0 %	0-12 months
Achkar	1997 Thromb Haemost	7.8 %	0-38 months
Rance	1997 Lancet	6.5 %	0-12 months
Prandoni	1992 NEJM	5.2 %	0-12 months
Nordström	1994 BMJ	4.8 %	0-6 months
Griffin	1987 Arch Int Med	4.0 %	0-12 months
Hettiarachchi	1998 Cancer	4.0 %	0-6 months
Baron	1998 Lancet	4.0 %	0-12 months
Goldberg	1987 Arch Int Med	3.7 %	0-12 months
Monreal	1988 Arch Int Med	3.6 %	not defined
Monreal	1997 Thromb Haemost	3.4 %	0-12 months
Cornuz	1996 Ann Int Med	2.5 %	0-12 months
Kirchmaier	1998 Internat. Angiol	2.0 %	0-6 months
Ahmed	1996 Angiology	1.5 %	not defined

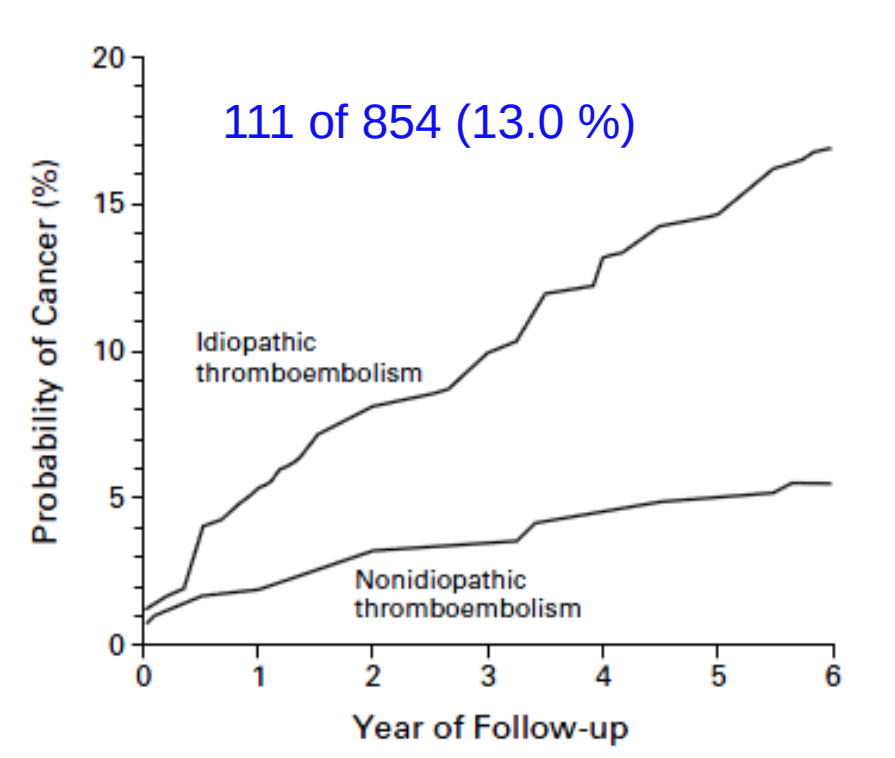
Thrombosis – an Announcement of Cancer

idiopathic thrombosis:	12.0 % (112/931)
	vs.
secondary thrombosis:	2.8 % (46/1644)

OR: 4.29 95% CI: 3.08 – 6.01; p < 0.0001

Cumulative Probability of Newly Diagnosed Cancer after a First Episode of Venous Thromboembolism

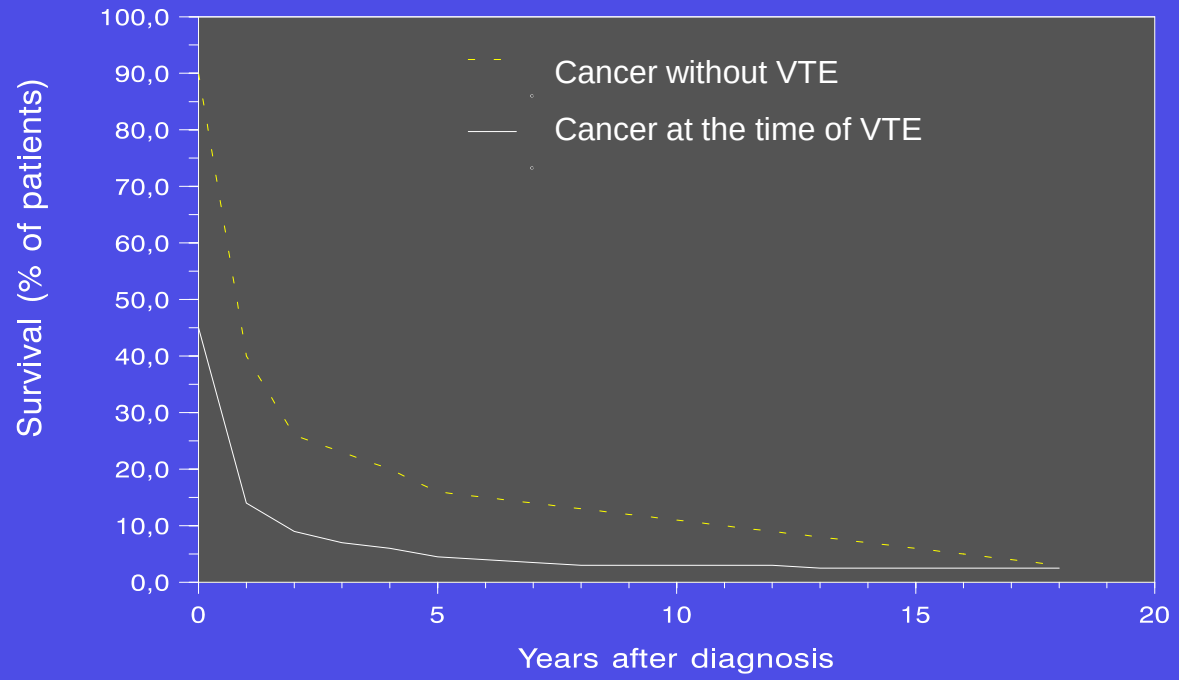
Schulman et al. N Engl J Med 2000; 342:1953-8



First Year: SIR 3.4; 95 % CI: 2.2 to 4.6)
Five Years: SIR 1.3 and 2.2

Thrombosis and Prognosis of Cancer

Sorensen et al. NEJM 2000; 343: 1846-50



No. At Risk				
Cancer at the time of VTE	668	23	10	3
Cancer without VTE	6668	913	338	87

Thrombosis incidence and Survival in Breast Cancer

Chew et al JCO. 2007; 25: 70-6

Table 2. Effect of Age, Race/Ethnicity, Comorbidities, Initial Cancer Stage, Histology, and Surgery on the Development of VTE Within 2 Years After Breast Cancer Diagnosis

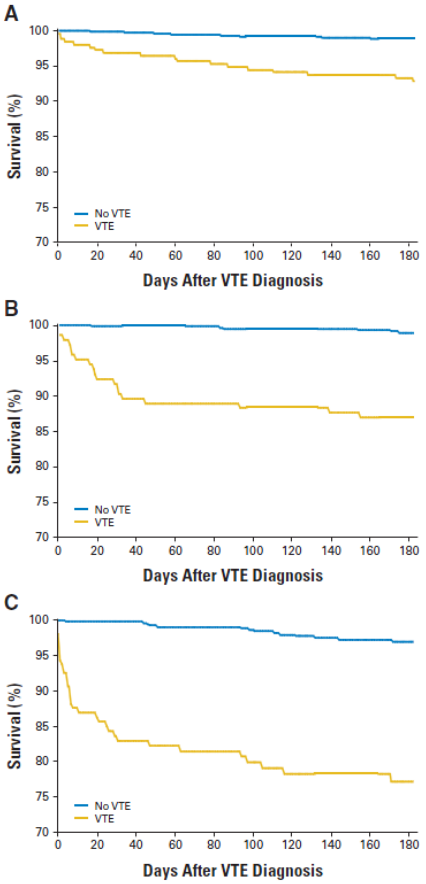
Variable	Hazard Ratio	95% CI	*P*
Age (*v* < 45), years			< .0001*
45-64	1.4	1.2 to 1.8	.0009
65-74	1.9	1.5 to 2.4	< .0001
>75	2.0	1.6 to 2.6	< .0001
Race/ethnicity (*v* white)			< .0001*
African American	1.3	1.0 to 1.5	.022
Hispanic	0.9	0.8 to 1.1	.49
Asian American	0.3	0.2 to 0.4	< .0001
No. of chronic comorbid conditions (*v* 0)			< .0001*
1	1.9	1.6 to 2.2	< .0001
2	2.3	1.9 to 2.7	< .0001
3	2.9	2.4 to 3.5	< .0001
SEER stage (*v* localized)			< .0001*
Regional	2.1	1.8 to 2.3	< .0001
Metastatic	6.3	5.3 to 7.5	< .0001
Histologic subtype (*v* adenocarcinoma)			.41*
Lobular	0.8	0.7 to 1.0	.09
Carcinoma NOS	1.2	0.9 to 1.6	.19
Mucinous	1.0	0.7 to 1.4	.91
Tubular	0.8	0.4 to 1.4	.43
Medullary	1.2	0.7 to 2.0	.52
Papillary	1.1	0.6 to 2.1	.77
Breast-related surgery			
Yes *v* no	0.6	0.5 to 0.7	< .0001

Abbreviations: VTE, venous thromboembolism, SEER, Surveillance, Epidemiology and End Results; NOS, not otherwise specified.
*Overall test of significance for polytomous variable.

DVT 6 months

DVT 7-12 months

DVT 13-24 months



108,255 patients with breast cancer - the 2-year cumulative VTE incidence: 1.2%,

National Institute for Health and Clinical Excellence

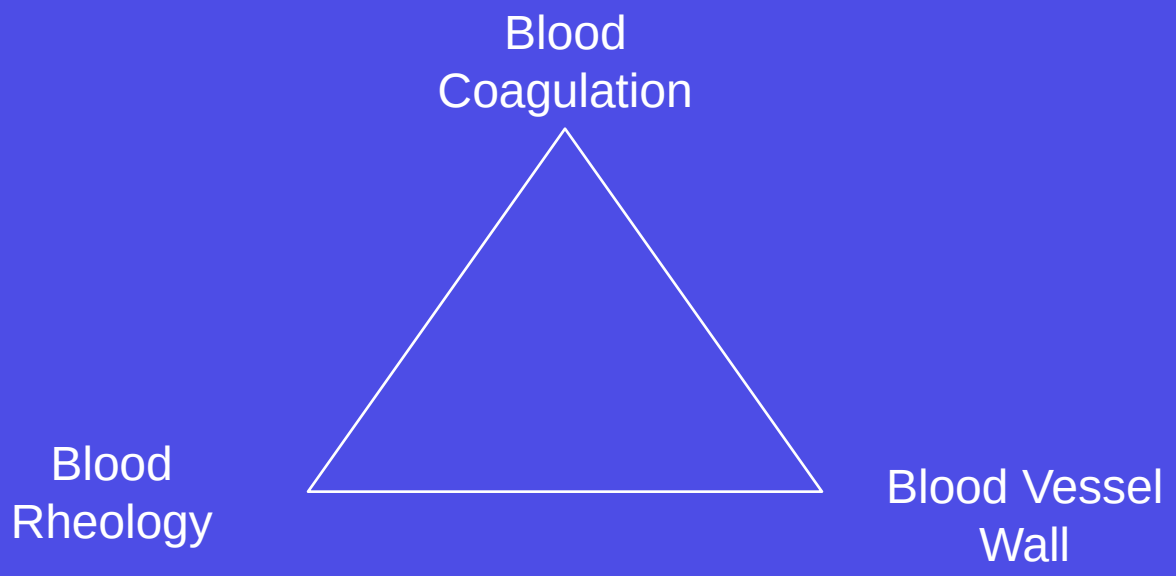
Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing

(Clinical guideline 144.) 2012. http://guidance.nice.org.uk/CG144

NICE recommends cancer tests for unexplained blood clots

Investigations for cancer should be carried out in patients aged over 40 who have a deep vein thrombosis or pulmonary embolism without an obvious cause, guidelines from the National Institute for Health and Clinical Excellence (NICE) recommend for the first time

Thrombosis



Hemostaseology and Cancer

- Deep Vein Thrombosis: ~ every 5_{th} cancer patient
- abnormal coagulation tests: ~ 60 % primary diagnosis of Cancer
  ~ 90 % with metastatic disease
- Abnormal rheological tests: ~ 70 - 80% of all cancer patients

Predisposing risk factors for thrombosis in malignancy

- age of patients (at primary diagnosis of cancer)
  median age - breast cancer: 57 years
  - endometrial cancer: 63 years
  - ovarian carcinoma: 61 years

- menopausal status
- obesity
- additional diseases (e.g. hypertension, metabolic, cardio vascular disorders)
- bed ridden
- iatrogenic therapeutic influences e.g. indwelling central venous catheter, cyto reductive treatment

Blood coagulation in Malignancy

- unspecific mechanism

  - Inflammation
  - functional aPC-Resistance
  - Hyper viscosity
  - Hypoxia
  - hereditary, acquired Thrombophilia ?

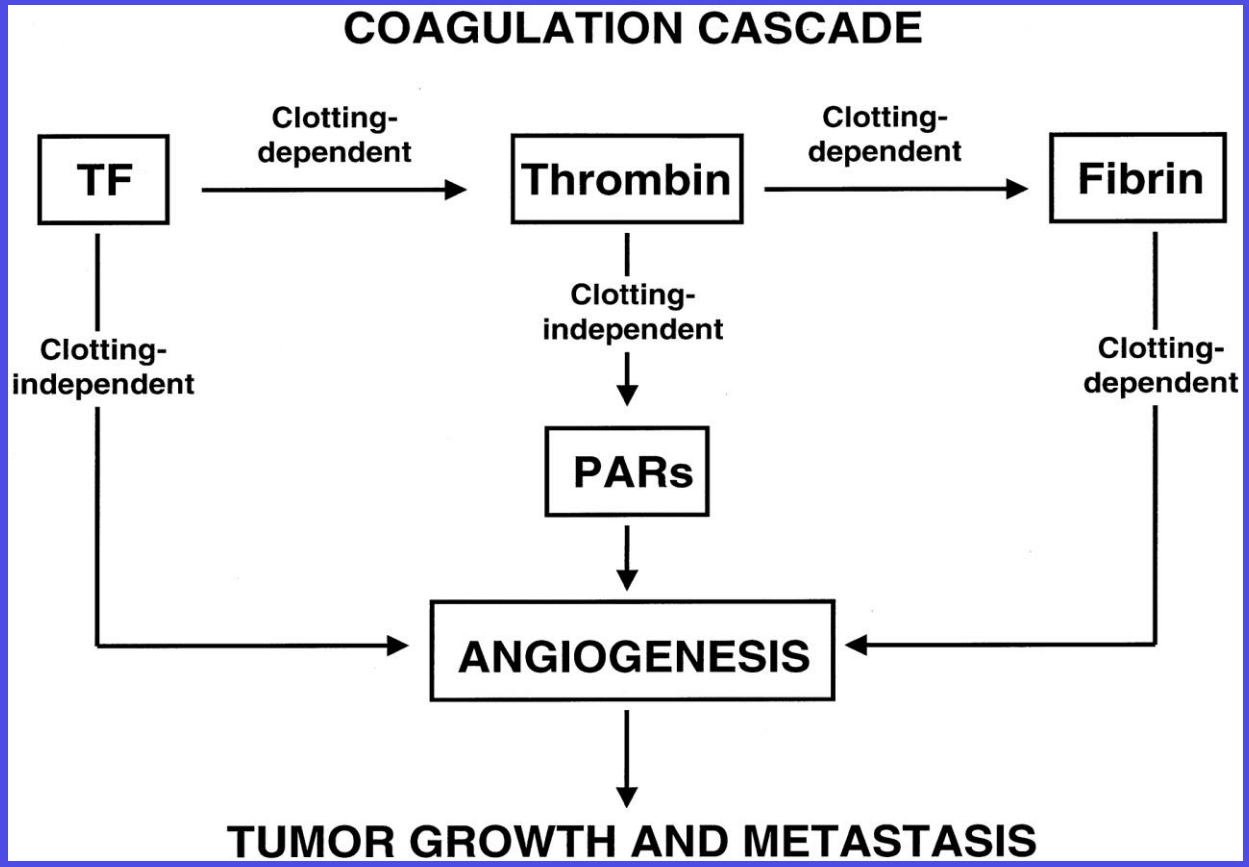
Blood coagulation in Malignancy

- tumor related mechanism

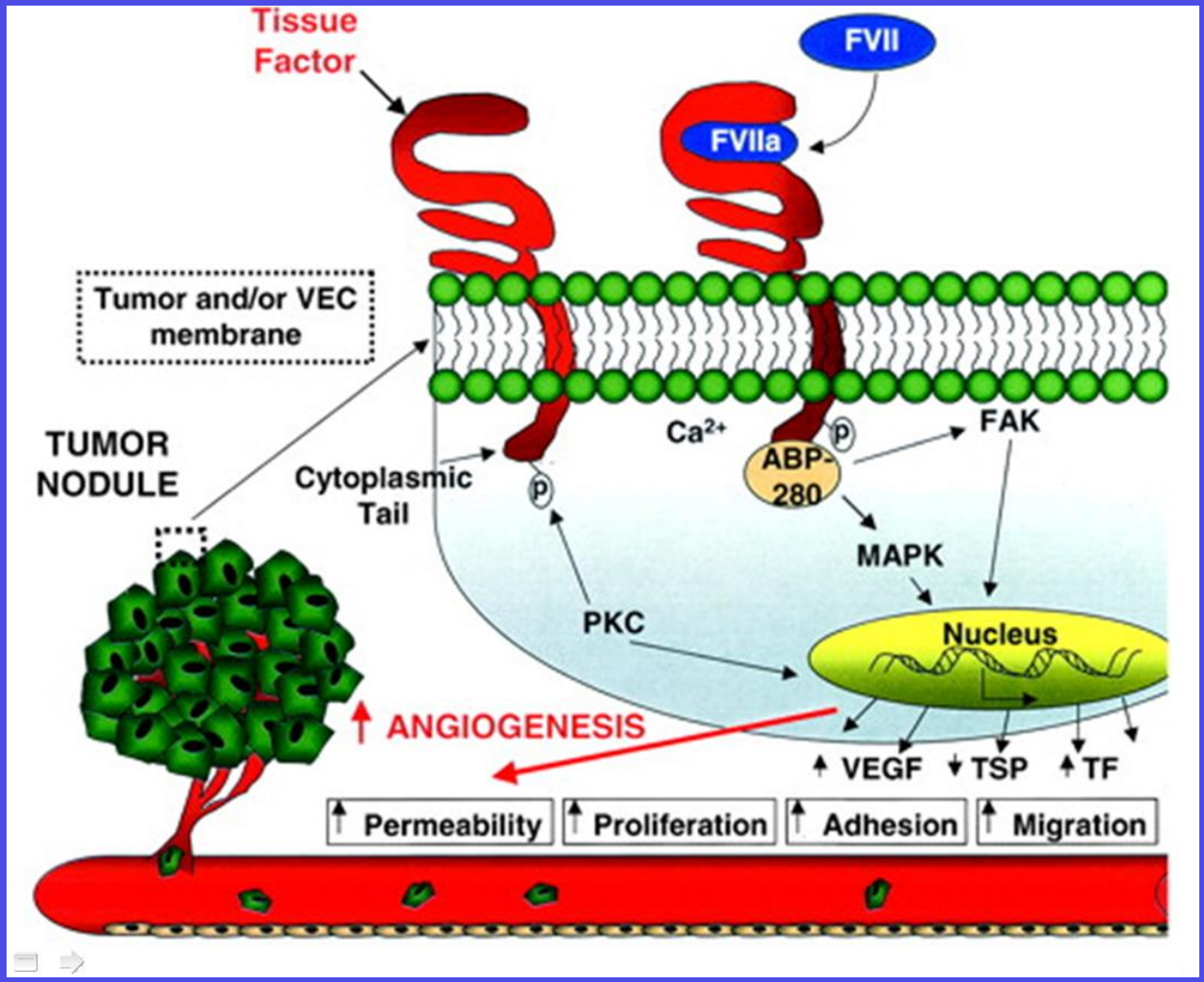
  - Tissue Factor /Tissue Factor-Microparticle (TF-MP)
  - Tumor Procoagulants
  - Prothrombin Receptor
  - PAI 1
  - Tumor vasculature

Coagulation Cascade, Angiogenesis, and Tumor growth and Metastasis

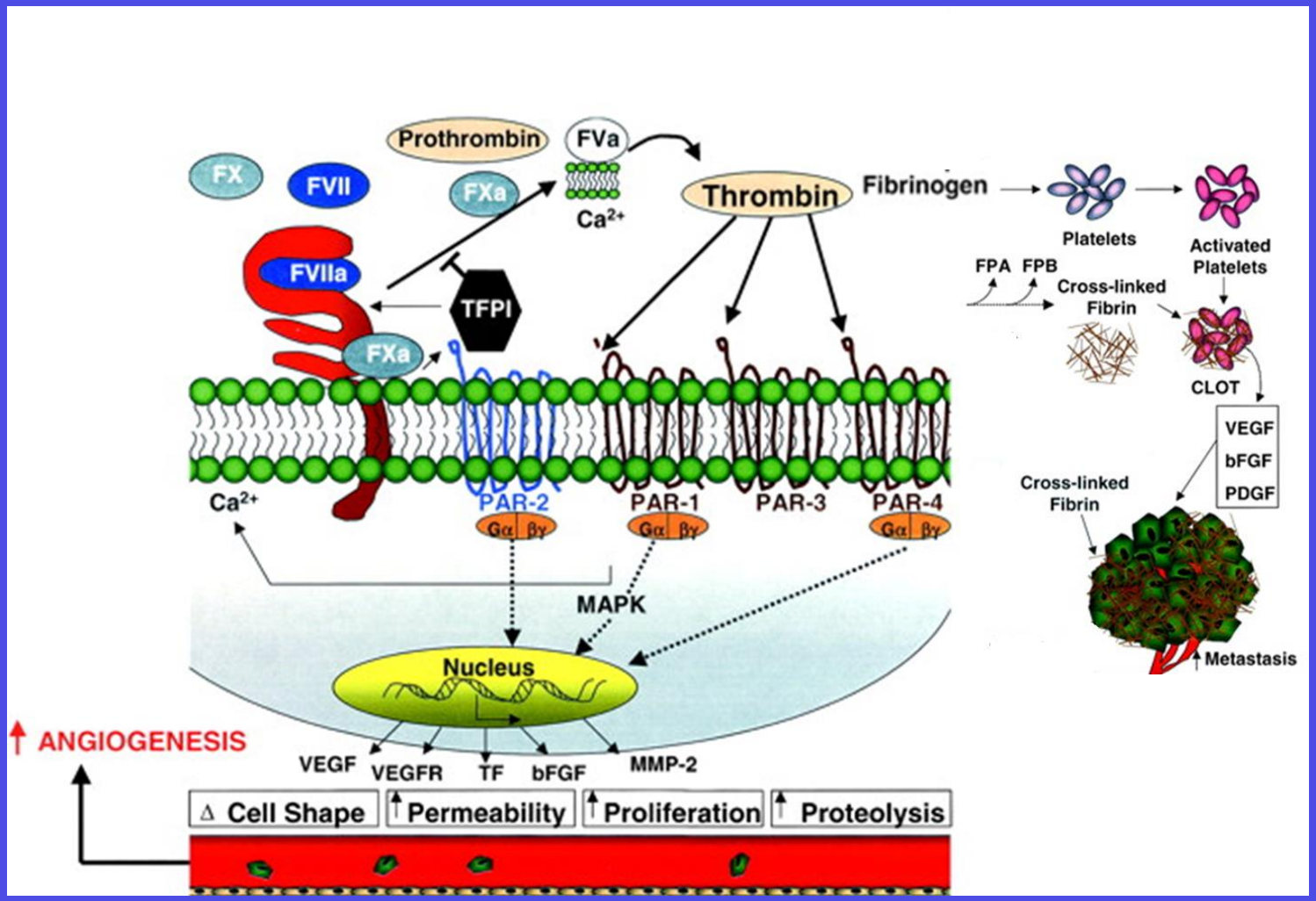
Rickles, FR et al. Chest 2003;124:58-*68S*



TF, Thrombin, and Tumor angiogenesis

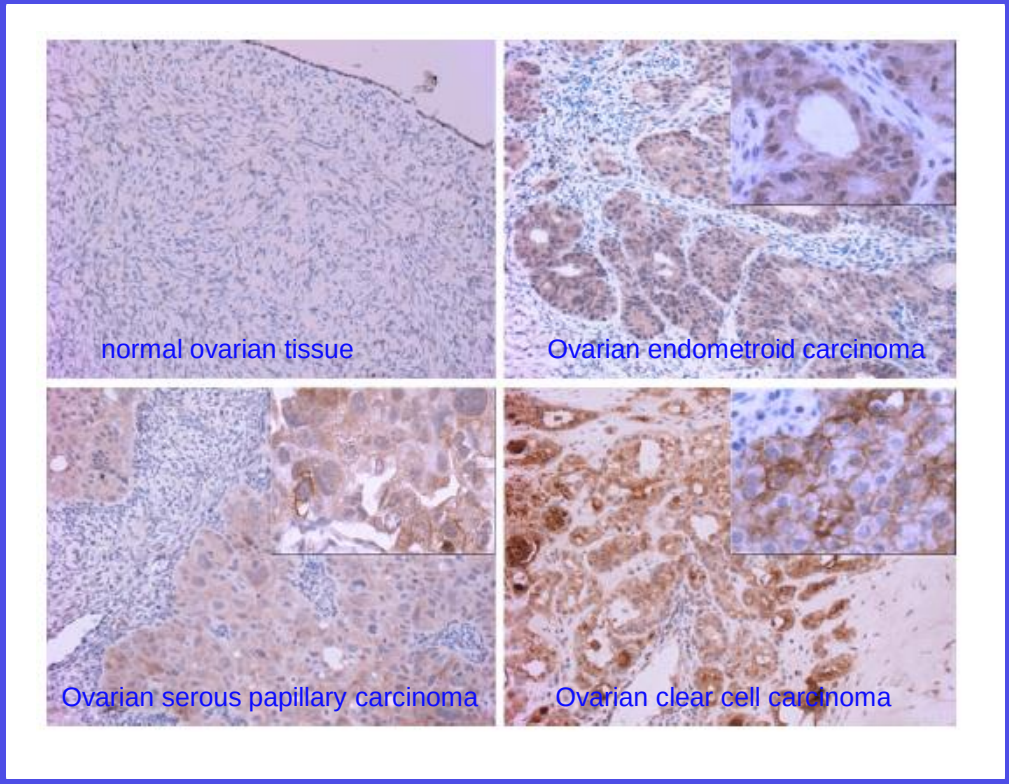


TF, Thrombin and Tumor angiogenesis



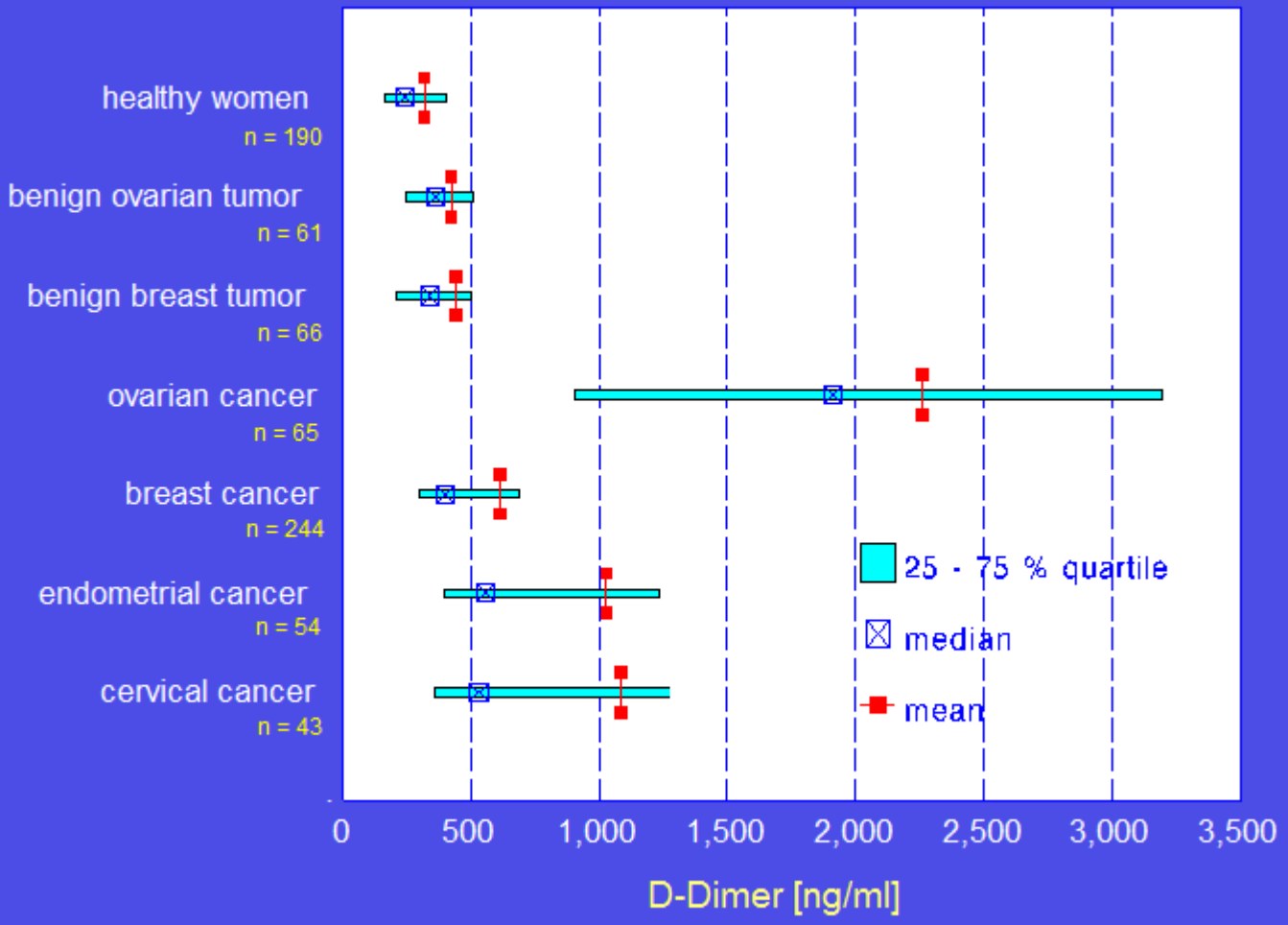
Tissue factor expression in Ovarian cancer

Cocco et al Clin Exp Metastasis 2011;28:689–700



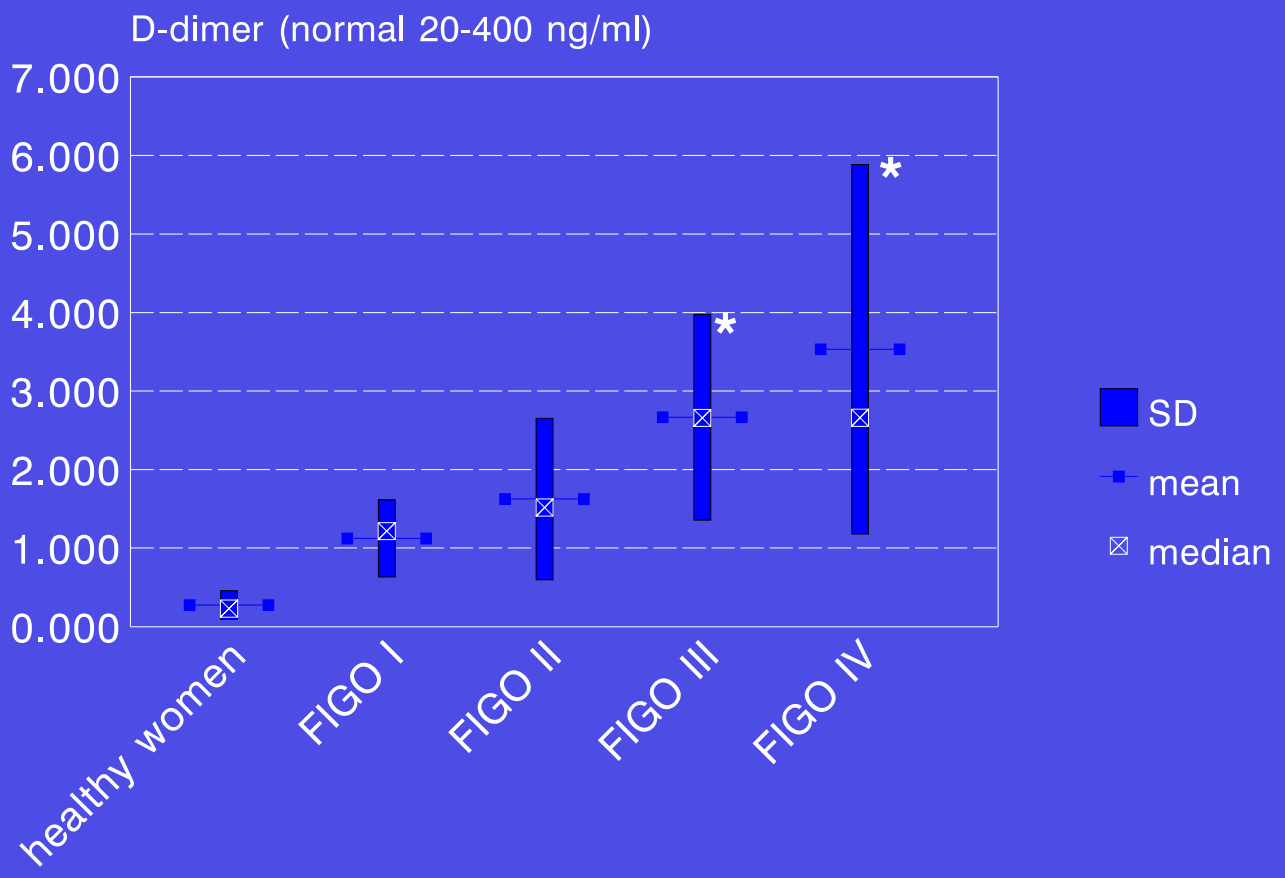
Pretreatment levels of the D-Dimer

Semin Thromb Hemost 2003; 29: 499-514



D-Dimer and Stage of Ovarian Cancer

Thromb.Haemost.1997;77:456-61



D-Dimer and stage of Ovarian cancer

Thromb.Haemost.1997;77:456-61

Prediction Thrombosis / Survival

- Preoperative Riskfactor Thrombosis (univariat)

  none

- Preoperative Riskfactor Overall survival (univariat)

FIGO Stadium	RR:	4,1 (95%KI: 2,0-8,3)	p<0.0001
D-dimer			p=0.002
CA 125			p=0.003
Fibrinogen			p=0.01

- Preoperative Riskfactor Overall survival (multivariate)

  FIGO Stage sole independent prognostic marker

Microparticle-associated tissue factor activity in 73 patients with pancreatic cancer and survival

Thaler J et al Eur J Clin Invest 2013 43:277-85

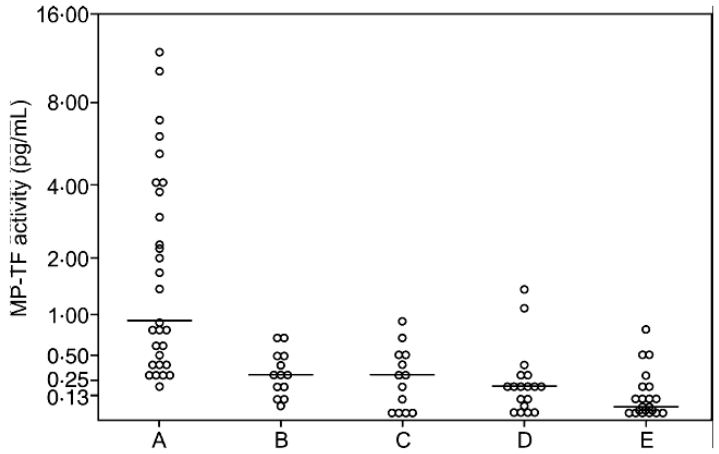


Figure 1 Levels of microparticle-associated tissue factor (MP-TF) activity in pancreatic cancer patients: (A) metastatic non-resectable cases (n = 29), (B) metastatic recurrent cases (n = 13), (C) localized unresected cases (n = 13), (D) localized resected cases (n = 18) and (E) healthy controls (n = 22). Bars indicate median MP-TF activity levels.

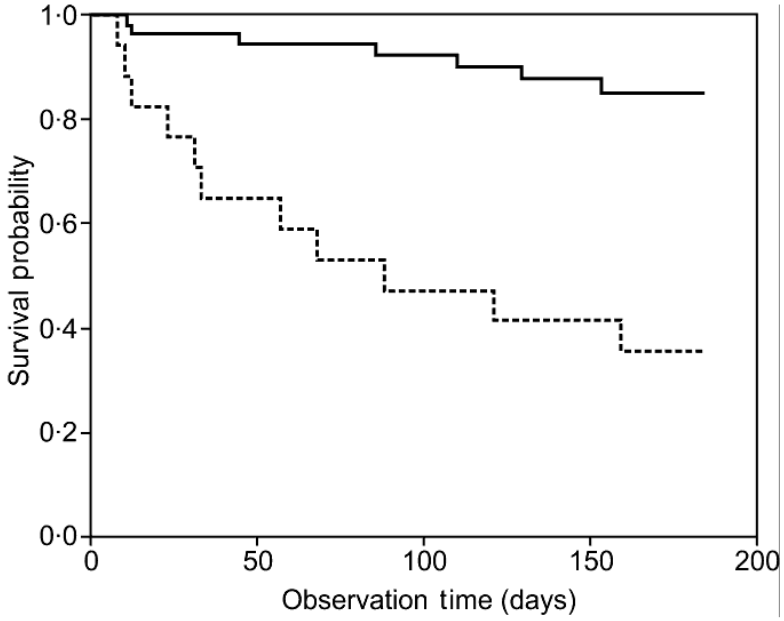
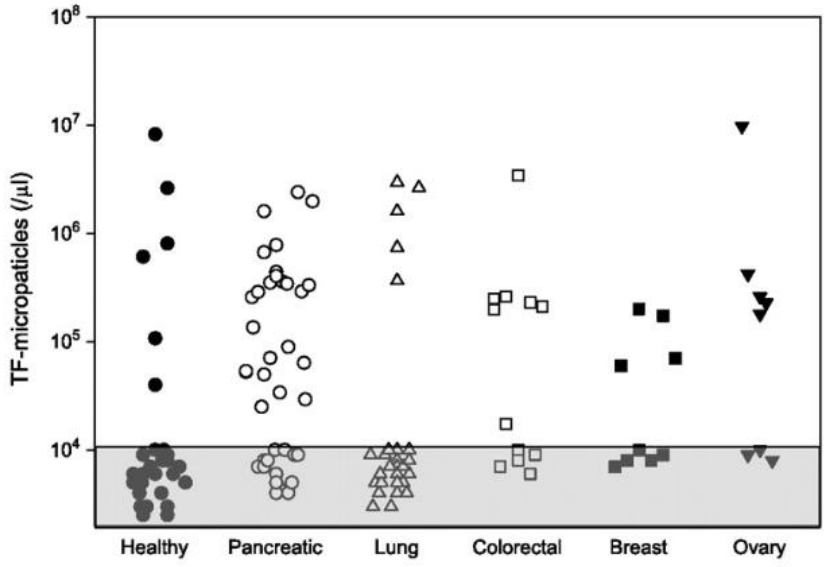


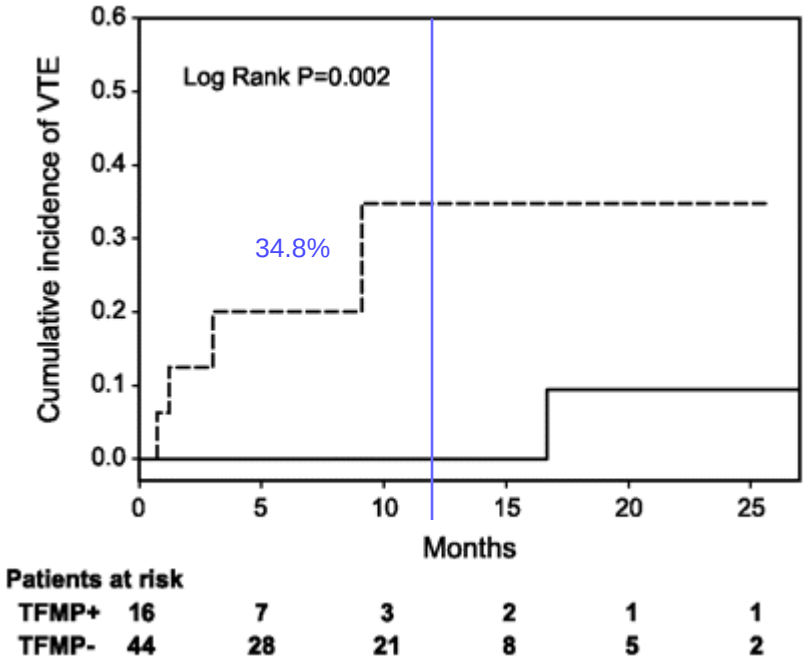
Figure 3 Kaplan–Meier estimates for cumulative survival probability in pancreatic cancer patients with microparticle-associated tissue factor activity below (continuous line) and above (dashed line) the 75th percentile (Log-rank test: $P < 0{\cdot}001$).

Tumor-Derived Tissue Factor–Bearing Microparticles and Venous Thromboembolic Events in Malignancy

Zwicker et al Clin Cancer Res 2009 15:6830-40



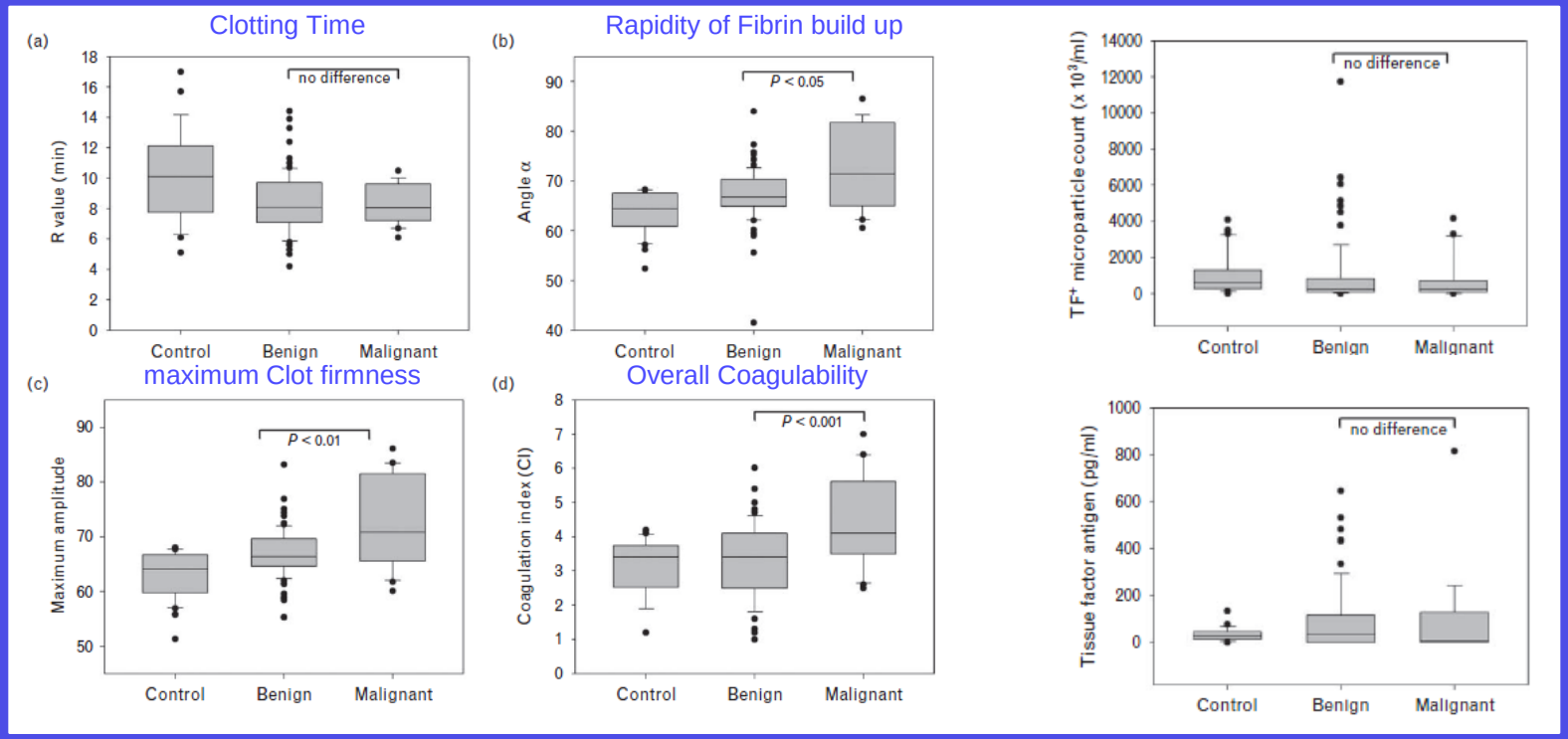
N=96



RR: 3.72; 95% CI: 1.18-11.76;P = 0.01

Blood clotting activation analysis for preoperative differentiation of benign versus malignant ovarian masses

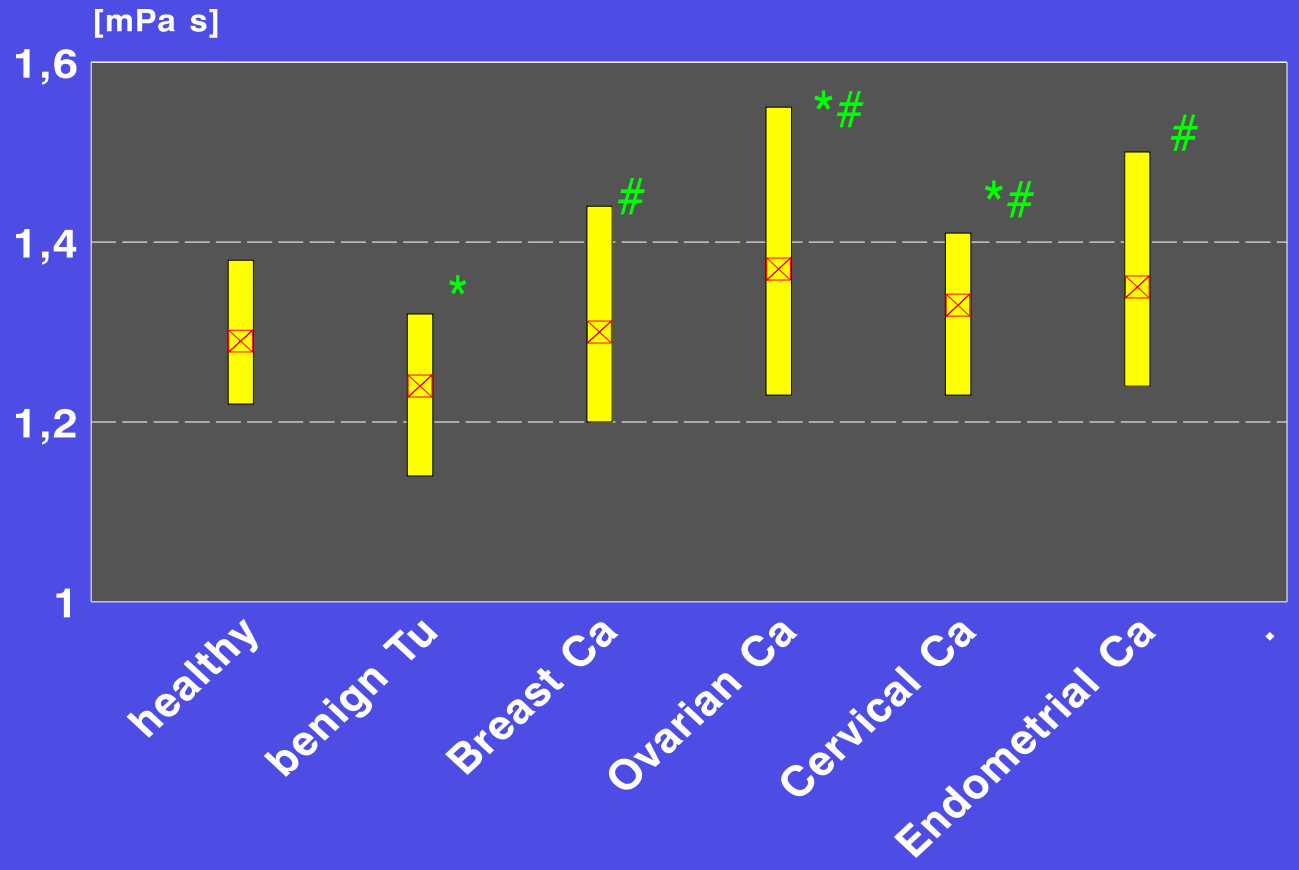
Amirkhosravi A et al. Blood Coag Fibrinol 2013, 24 (in press)



Thrombelastography, D-Dimer and TF-Ag, TF-MP

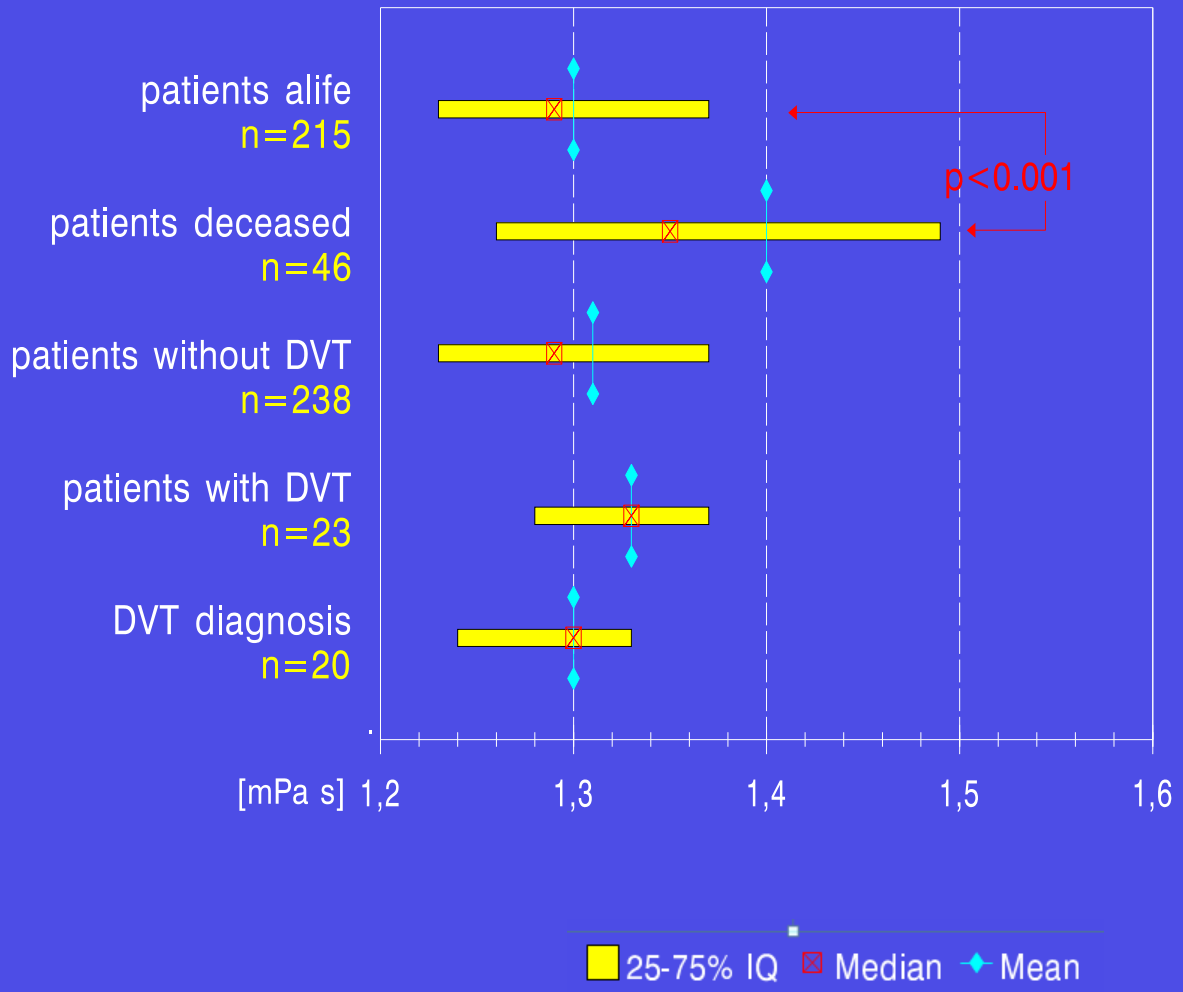
Plasma viscosity

Semin Thromb Hemost 2003; 29: 499-514

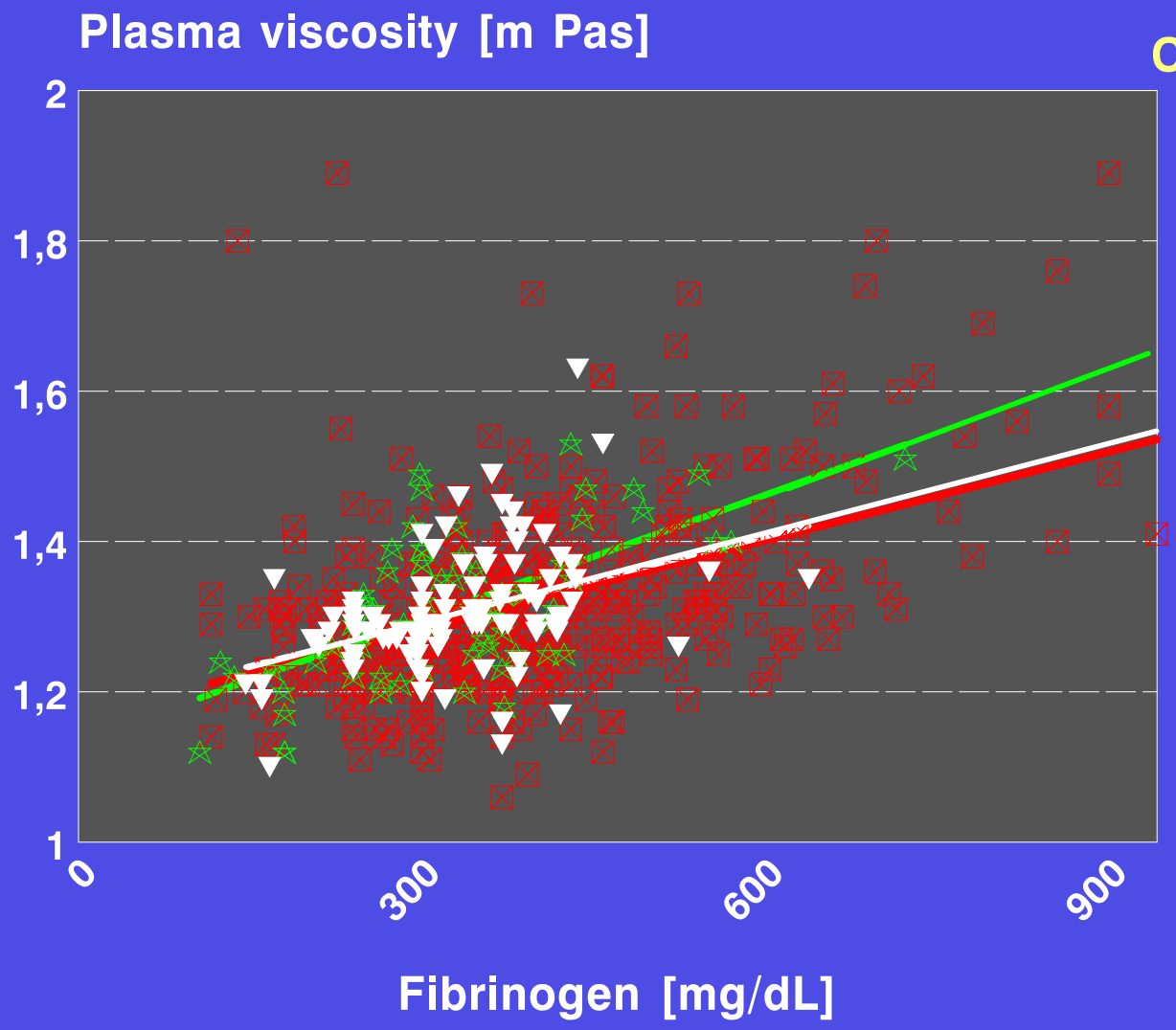


Plasma viscosity in Breast Cancer

Semin Thromb Hemost 2003; 29: 499-514



Correlation between plasma viscosity and fibrinogen in healthy women, and patients with benign and malign breast tumors

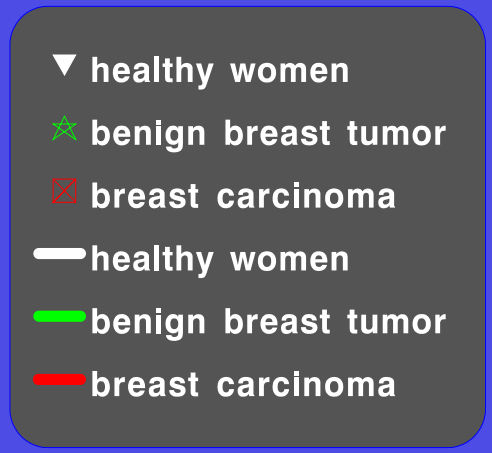


Correlation coefficients (r)

healthy women: r = 0.38; p < 0.0001

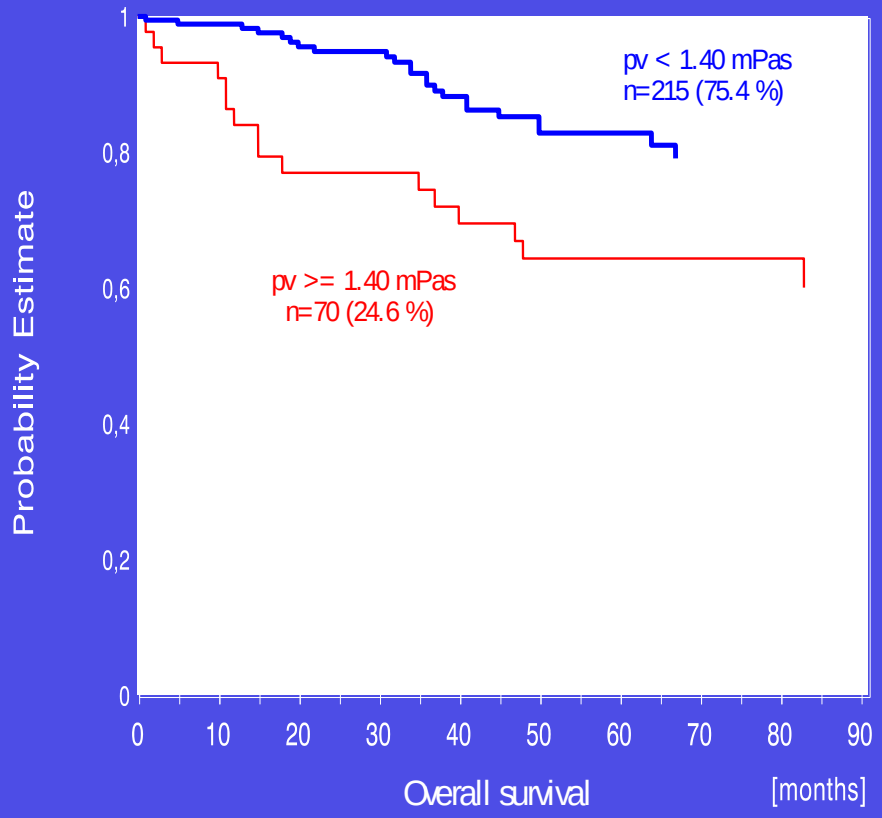
benign breast tumor: r = 0.53; p < 0.0001

breast carcinoma: r = 0.36; p < 0.0001



Plasma viscosity the day before Surgery in 285 Patients with localized Breast Cancer

Semin Thromb Hemost 2003; 29: 499-514



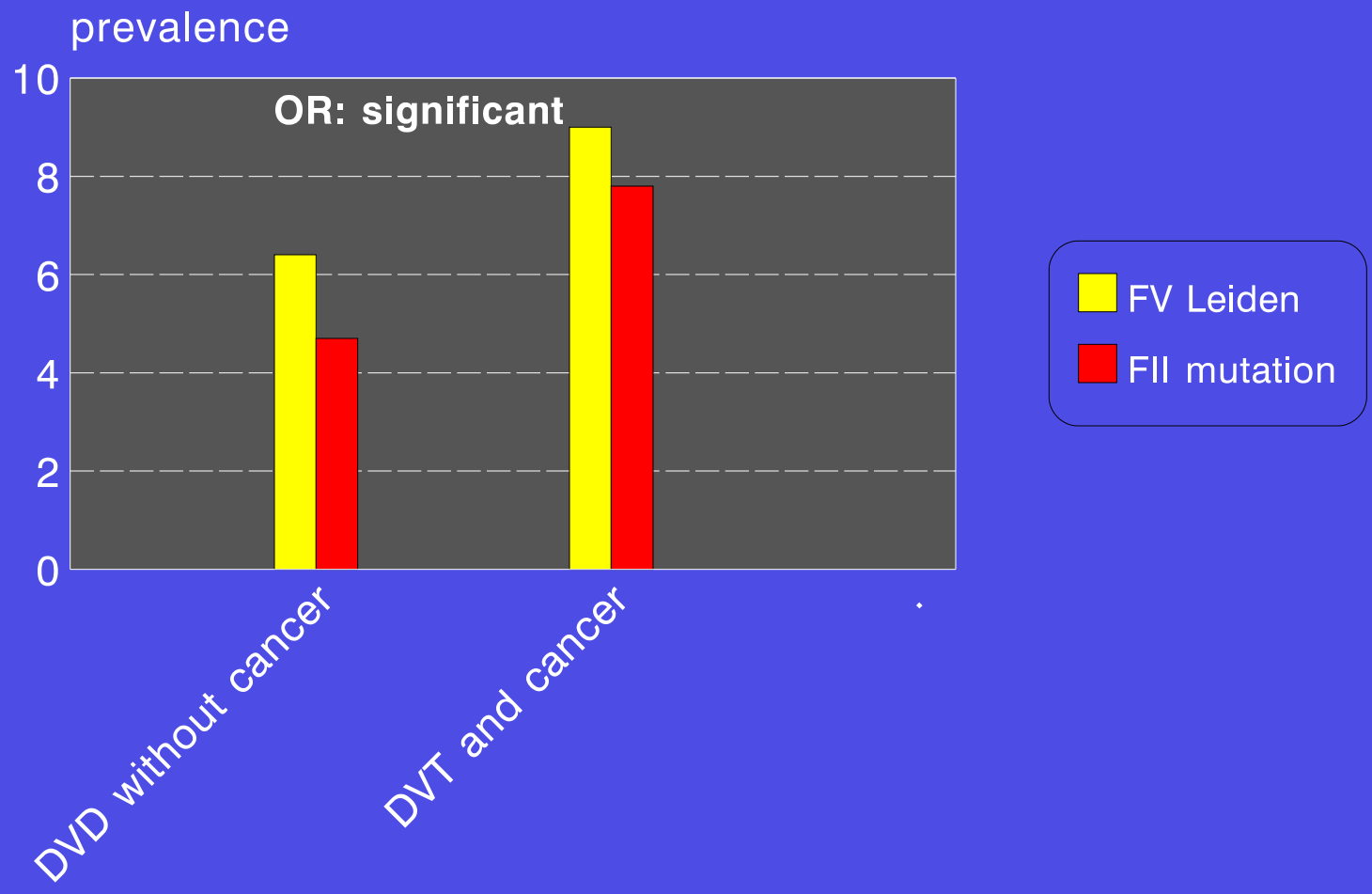
Prevalence of FVL, FII G20210A, MTHFR C677T and FXIII Val34Leu polymorphisms in 211 cancer patients with and without VTE

Ramacciotti E Thromb Res 2003;109;171– 4

Genotype	With thrombosis ($n=64$)	Without thrombosis ($n=147$)	Odds ratios (CI 95%)
FVL (heterozygous)	1 (1.5%)	4 (2.7%)	0.6 (0.06–5.35)
FII G20210A (heterozygous)	1 (1.5%)	2 (1.3%)	1.2 (0.10–13.13)
MTHFR C677T			
Heterozygous	29 (45.3%)	67 (45.5%)	
Homozygous	5 (7.8%)	22 (14.9%)	
Heterozygous + homozygous	34 (53.1%)	89 (60.5%)	0.8 (0.40–1.38)
FXIII Val34Leu			
Heterozygous	16 (25.0%)	36 (24.4%)	
Homozygous	3 (4.6%)	6 (4.1%)	
Heterozygous + homozygous	19 (29.6%)	42 (28.5%)	1.0 (0.55–2.01)

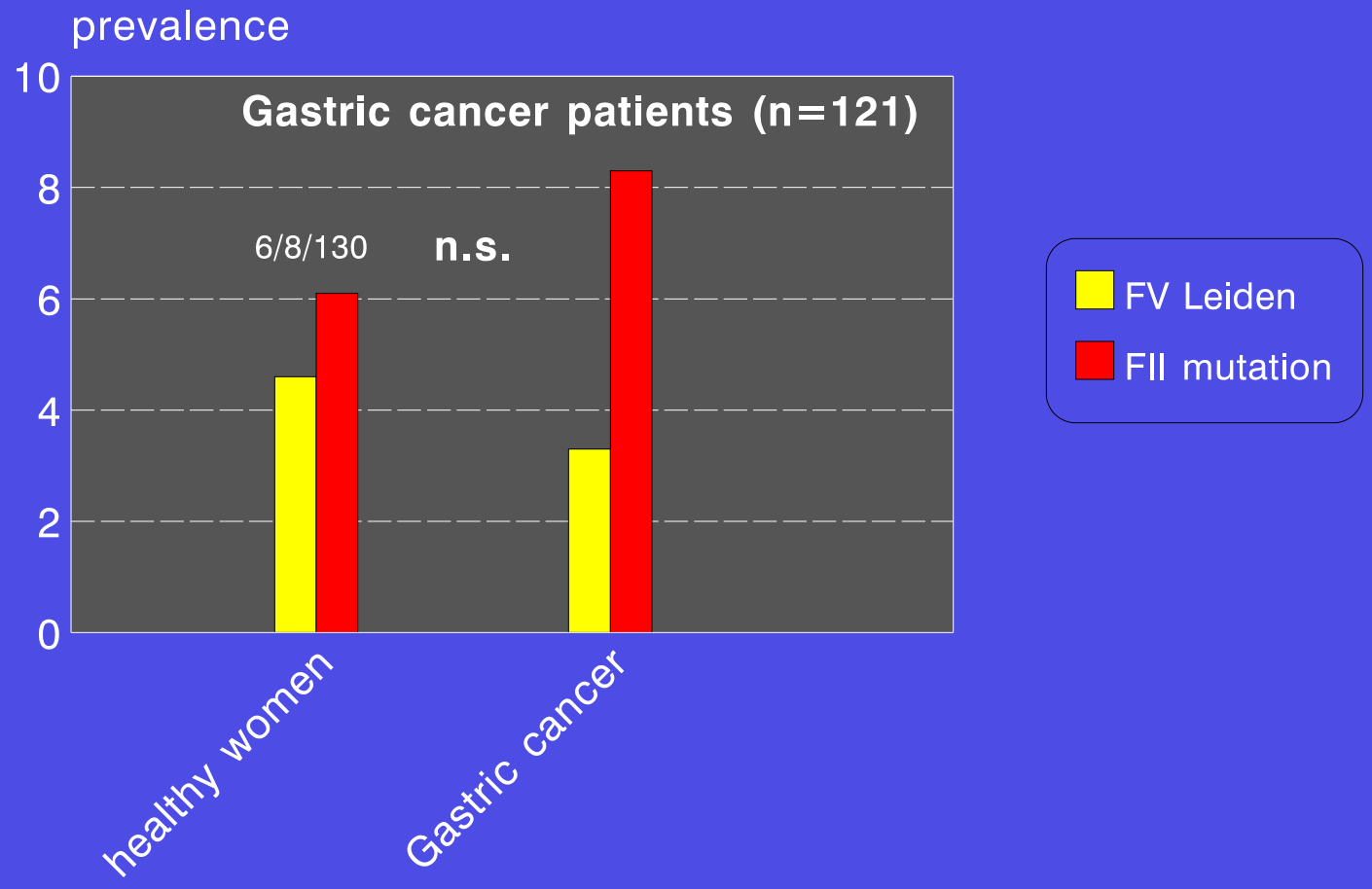
Thrombophilia and Thrombosis in patients with (n=178) and without Cancer (n=2528)

Blom et al YAMA 2005;293:715-22



Factor V Leiden and FII mutation in Cancer

Battistelli et al World J Gastroenterol 2006:12;4179-80



Risk assessment for cancer-associated thrombosis: What is the best approach?

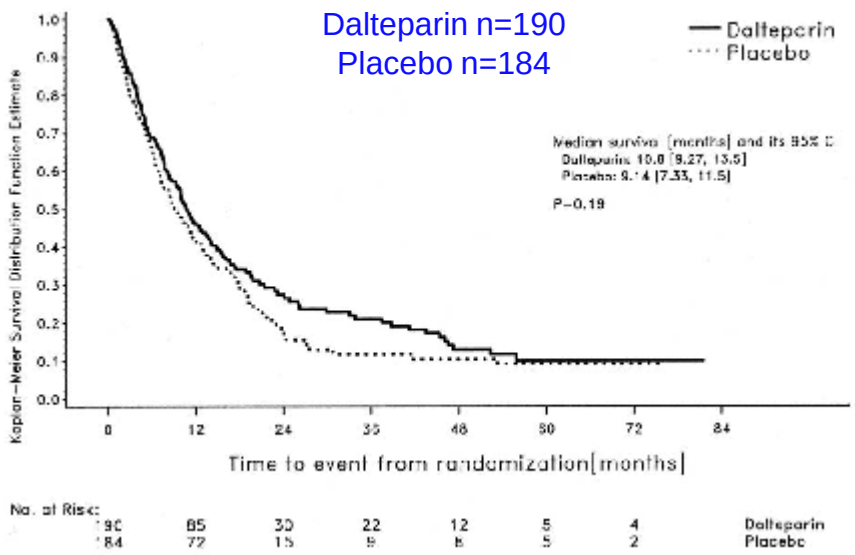
Khorana AA Thromb Res 2012 129, Suppl 1:S10–S15

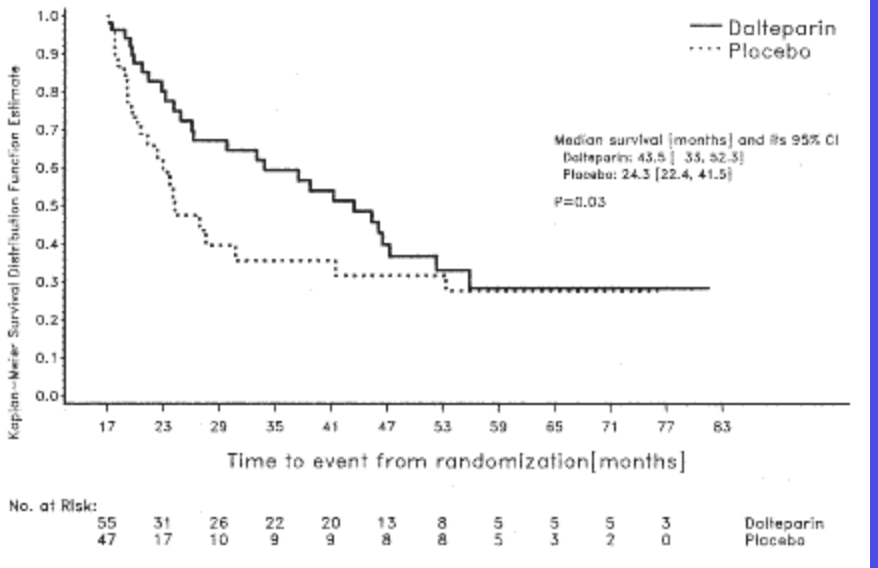
Patient characteristics	Risk score*
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count 350,000/mm^3 or more	1
Hemoglobin level less than 10 g/dl or use of red cell growth factors	1
Prechemotherapy leukocyte count more than 11,000/mm^3	1
Body mass index 35 kg/m^2 or more	1

* Risk scores: High risk ≥3; intermediate risk = 1–2; low risk = 0.

Low Molecular Weight Heparin, Therapy With Dalteparin, and Survival in Advanced Cancer: The Fragmin Advanced Malignancy Outcome Study (FAMOUS)

Kakkar AJ J Clin Oncol 22:1944-8

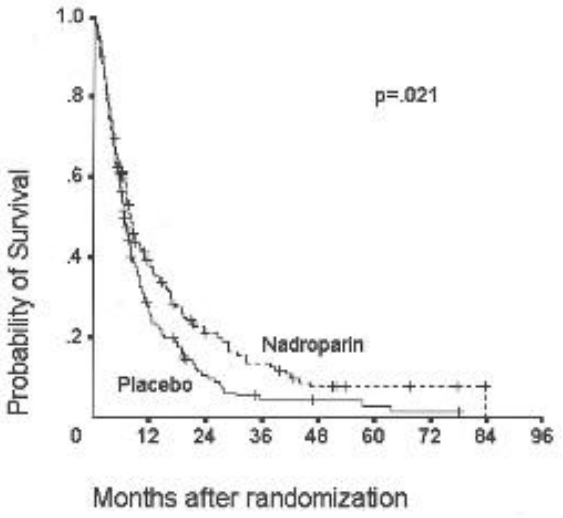


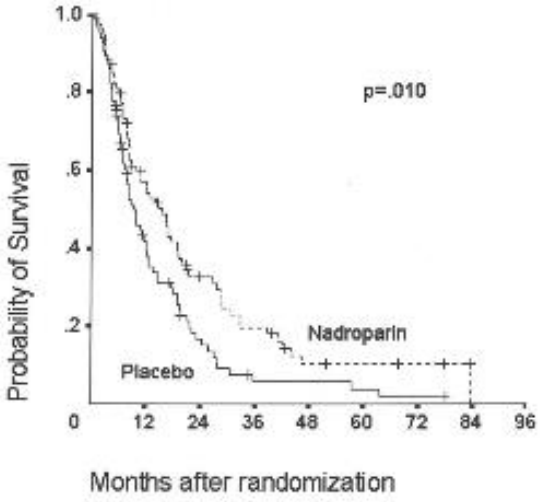


Dalteparin (5,000 IU) or placebo for 1 year

The Effect of Low Molecular Weight Heparin on Survival in Patients With Advanced Malignancy)

Klerk CPW *J Clin Oncol 23:2130-5*





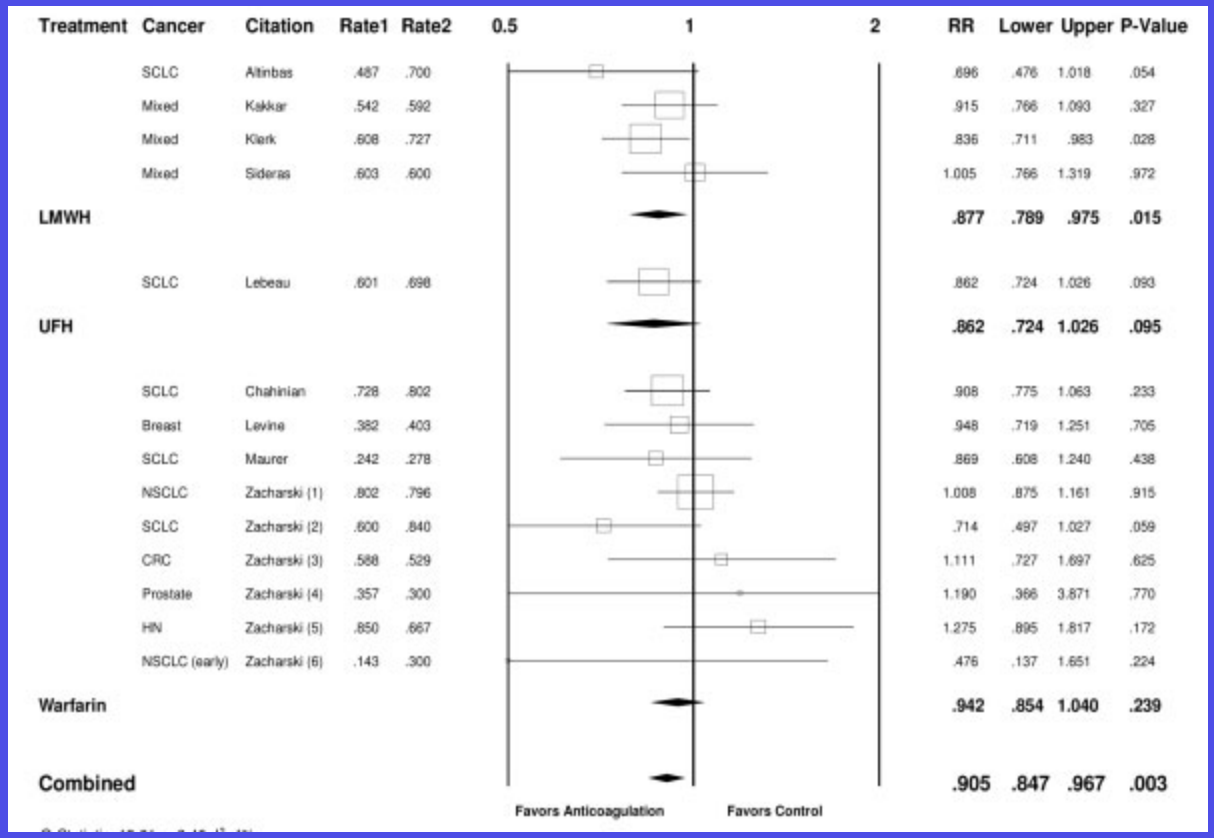
No. at risk							
Nadroparin	148	51	23	15	7	4	3
Placebo	154	36	12	4	3	2	1

No. at risk							
Nadroparin	79	41	20	12	5	4	3
Placebo	85	31	11	3	3	2	1

Nadroparin or placebo for 2 + 4 weeks

A meta-analysis and systematic review of the efficacy and safety of anticoagulants as cancer treatment: impact on survival and bleeding complications

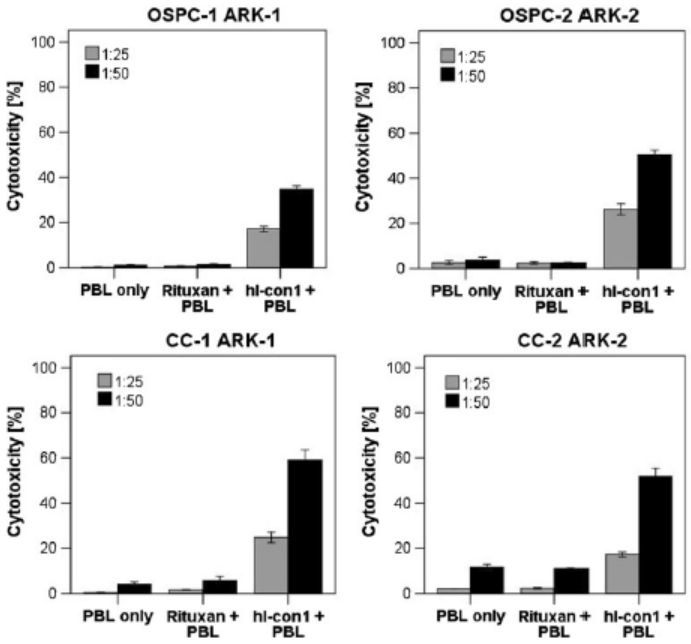
Kuderer NM Cancer 2007;110:1149–60



Tissue factor expression in ovarian cancer: implications for immunotherapy with hI-con1, a factor VII-IgGF$_c$ chimeric protein targeting tissue factor

Cocco et al Clin Exp Metastasis 2011;28:689–700

hI-con1 molecule induces strong cytotoxicity against primary chemotherapy-resistant ovarian cancer cell lines overexpressing TF and may represent a novel therapeutic agent for the treatment of ovarian tumors refractory to standard treatment modalities.



Hemostaseology and Cancer

- Anticoagulants may influence biologic mechanism in some tumor type.
- Tissue Factor may be a targed for Immunetherapy.
- The ideal predictive marker for the development of DVT in Cancer is yet to be found.
- Screening for Cancer is recommended in patients aged over 40 with unprovoked DVT / PE (NICE).